REVIEW

Cigarette Smoking

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Cigarette smoking is the largest preventable risk factor for morbidity and mortality in developed countries. Dramatic changes in the prevalence of cigarette smoking in the second half of this century in the United States (i.e., a reduction among men and an increase among women) have reduced current smoking levels to approximately one quarter of the adult population and have reduced differences in smoking prevalence and smoking-attributable diseases between the sexes. Current smoking in the United States is positively associated with younger age, lower income, reduced educational achievement, and disadvantaged neighborhood environment. Daily smokers smoke cigarettes to maintain nicotine levels in the brain, primarily to avoid the negative effects of nicotine withdrawal, but also to modulate mood. Regular smokers exhibit higher and lower levels of stress and arousal, respectively, than nonsmokers, as well as higher impulsivity and neuroticism trait values. Nicotine dependence is the single most common psychiatric diagnosis in the United States, and substance abuse, major depression, and anxiety disorders are the most prevalent psychiatric comorbid conditions associated with nicotine dependence. Studies in twins have implicated genetic factors that explain most of the variability in vulnerability to smoking and in persistence of the smoking phenotype. Future research into the causes of smoking must take into account these associated demographics, social factors, comorbid psychiatric conditions, and genetic factors to understand this complex human behavior. [J Natl Cancer Inst 1999;91:1365–75]

Cigarette smoking, hereafter referred to as "smoking," is the largest single risk factor for premature death in developed countries. Approximately one fifth of the deaths in the United States are attributable to smoking, and 28% of the smoking-attributable deaths involve lung cancer, 37% involve vascular disease, and 26% involve other respiratory diseases *(1)*. More than 400 000 deaths per year and 30% of all cancers in the United States are attributable to smoking *(2)*. Lung cancer is the largest single cause of cancer-associated mortality *(3)* and is the most common cause of smoking-related mortality in the United States *(4)*. The attributable risk from smoking for oral, pharyngeal, and esophageal cancers is substantial, although less than that for lung cancer *(5,6)*. The attributable risk from both smoking and alcohol consumption accounts for the majority of both oral and pharyngeal cancers *(5)* and of esophageal cancer *(7)*. Morbidity and mortality attributable to smoking would decline in the future if reductions in smoking prevalence were to be observed. However, despite dramatic declines in adult male smoking prevalence in the United States observed from the 1960s through the 1990s *(8)*, the decline in current adult smoking prevalence slowed by about 1990 *(9)*, and recent surveys of current smoking in youth, defined as cigarette use on at least one of the last 30 days preceding the survey, show a statistically significant increase (from 27.5% in 1991 to 36.4% in 1997) *(10)*. The prevalence of current smoking among adults in the United States, defined as smoking daily or smoking on some days *(11)*, is now about 23% in women and 27% in men and is statistically significantly higher in those less than 65 years of age; in those with 9–11 years of education; in those below the poverty threshold; in whites, blacks, and American Indians/Alaskan Natives; and in military veterans *(9,12–15)*. Projected demographic and smoking prevalence trends suggest that the absolute number of current smokers in the United States, about 47 million individuals in 1995, will continue to increase, especially in those below the poverty threshold, in those with less than 13 years of education, and in those greater than or equal to 65 years of age *(9,15–18)*.

Smoking prevalence in men worldwide is higher than it is in the United States, while smoking prevalence among women worldwide is usually less than the prevalence in men, although it has equaled or exceeded that in men in some northern European countries *(19,20)*. While annual per capita cigarette consumption has dropped in developed countries from a high of more than 3000 in the 1970s to about 2600 in 1990, it is increasing in developing countries (260% increase in China between 1970 and 1990), so that worldwide annual per capita cigarette consumption has not changed substantially over the last 25 years *(20)*. Because of the delayed health effects of smoking, morbidity and mortality in developing countries attributable to smoking have not yet surpassed those in developed countries but are likely to do so in the next century *(20,21)*.

The study of biomarkers in smoking-attributable cancer has concentrated on measures of exposure (i.e., cotinine, NNAL-Gluc[1]), dose (i.e., carcinogen–macromolecular adducts, such as 4-amino biphenyl hemoglobin adducts), micronutrients (i.e., β-carotene), and genetic factors that may modify these factors or their effects *(22)*. The investigation of such biomarkers is predicated on the assumption that an enhanced understanding of metabolic mechanisms will help to identify susceptible groups or individuals and direct future research or prevention efforts. Another group of risk factors for lung cancer and other smoking-related cancers are those that are associated with smoking, its initiation, and its persistence. We will review factors associated with current and persistent smoking that have been studied by use of pharmacologic, epidemiologic, behavior genetic, psychologic, and psychiatric perspectives. The identification of those

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factors consistently and statistically significantly associated with smoking will provide biologic and social variables with which to investigate mechanisms that contribute to the persistence of this behavioral phenotype. Improved understanding of these mechanisms may enable improved cancer prevention and control efforts.

METHODS

The purpose of this review is to describe and evaluate demographic, psychosocial, and biologic factors found to show statistically significant associations with current and persistent cigarette smoking in order to make research recommendations concerning which covariates are important in the study of the human phenotype of cigarette smoking. Published English-language papers of all types were collected over a 12-month period from October 1997 to October 1998 by use of the portion of the MEDLINE® database from 1985 to the present and various combinations of the following terms: smoking, smoking cessation, epidemiology, prevalence, nicotine, cotinine, acetylcholine, nicotinic acetylcholine receptors, lung cancer, oral cancer, drug abuse and dependence, alcohol dependence, depression, twin studies, and animal model studies. Reports from the Surgeon General, monographs, and internet sites were also searched for relevant studies and evaluated for inclusion in this review. The purpose of the search was to gather studies on the cigarette smoking phenotype from the epidemiologic, pharmacologic, psychiatric, and psychologic literature. Studies evaluated for associated factors included the following: case–control and case–case studies of demographic, genetic, psychiatric, and psychologic variables; factor analyses of case series; twin studies; and animal model studies. To distinguish between studies included or excluded, the criteria of sample size, validated or controlled measures of phenotype, established analytic approaches, and reasonable interpretation were used for evaluation. The narrative method was used to provide examples of the evidence presented in the studies reviewed. The method used to make research recommendations was to identify those phenotypes that were consistently and statistically significantly associated with current cigarette smoking.

SMOKING AND NICOTINE

Addiction to nicotine has been established as the psychopharmacologic mechanism that maintains cigarette smoking behavior *(23)*. Nicotine activates the brain's mesolimbic dopaminergic reward system *(24,25)* and produces dependence resulting in physical and neurobiologic withdrawal symptoms on abrupt cessation *(26,27)*. In rodent and primate animal models of drug addiction, once study subjects are trained in a controlled schedule paradigm to avoid the aversive effects of high concentrations of nicotine, nicotine is self-administered *(28–31)*. Nicotine acts as an agonist for neuronal nicotinic acetylcholine receptors (nAChRs)—pentameric ionotropic (Na^+ and Ca^{2+}) receptors found presynaptically throughout the central nervous system (CNS) and postsynaptically in the autonomic nervous system—that modulate the release of neurotransmitters and ganglionic potentials *(32)*. After chronic nicotine treatment *(33–35)*, nAChR numbers are increased, particularly the most common nAChR type in the mammalian brain, the $\alpha4\beta2$ heteromer *(36,37)*. The increased numbers of nAChRs upon chronic nicotine treatment is associated with the development of behavioral tolerance to nicotine in animal models and is statistically significantly related to intensity and duration of smoking history in human postmortem brain *(34,38)*. Nicotine also acts as an antagonist, not because the increased numbers of nAChRs are associated with an increase in nAChR messenger RNA *(39,40)* or a change in binding parameters of nicotine to the receptor *(33–35)* but rather because of a reduction in nAChR turnover and accumulation of nAChR at the cell surface *(41)*. Short- and long-term desensitization kinetics of $\alpha4\beta2$ receptor suggest that desensitization and inactivation are two different allosteric states that may be responsible for the acute and chronic nicotine tolerance observed in humans and in animals *(41,42)*.

Smokers of cigarettes increase smoking intensity, smoking rate, or inhalation to maintain levels of nicotine, as measured by plasma levels of nicotine in both *ad libitum* and laboratory smoking settings *(43–46)*. Measured nicotine levels in the arterial and venous circulation indicate that individual smokers can obtain plasma nicotine levels of 20–50 ng/mL *(46–48)*. This concentration range (≈100–300 n*M*) is one order of magnitude less than the equilibrium binding and activation concentration of *l*-nicotine to the $\alpha4\beta2$ receptor, the predominant nAChR in the brain, but is nearly equal to the effective concentration for inactivation and accumulation of the $\alpha4\beta2$ receptor *(49,183)*. Nicotine absorption per cigarette has been measured both by graphical methods from nicotine concentration curves obtained from plasma blood measurements *(46)* and by parametric calculation by use of stable isotope studies of nicotine to cotinine conversion and nicotine and cotinine clearance values obtained in inpatient-infusion studies *(47)*. These studies suggest that smokers are extracting approximately 1–2 mg of nicotine per cigarette. The total amount of nicotine per cigarette measured by smoking machines by use of human smoking parameters of puff volume, duration, and frequency is about 2–3 mg per cigarette *(50,51)*, suggesting that smokers absorb more than half of the inhaled nicotine. However, none of these methods measures the peak brain concentration of nicotine, which is presumed to be the major pharmacologic factor that mediates reward, dependence, and the development of tolerance. Studies of dosing kinetics in animal models demonstrate the development of higher levels of tolerance with higher peak concentrations *(31,52)*.

One behavioral mechanism responsible for differences in nicotine consumption may be related to variation in nicotine and cotinine metabolism *(53–55)*. Nicotine from tobacco smoke is absorbed quickly (in seconds) throughout the body on initial dosing *(46,48)* and then is eliminated with a half-life of 2–3 hours *(56)*. Nicotine is metabolized principally (≈80%) to cotinine by cytochrome P450 2A6 *(47,57,58)*, which is also responsible for much of the metabolism of cotinine *(59)* and for much of the activation of the potent tobacco smoke carcinogen NNK *(60)*. The typical smoker experiences a nicotine concentration nadir in the morning after overnight abstinence and then smokes to increase nicotine levels over the first few hours of the day and to maintain a plateau throughout the remainder of the day *(46)*. Clearance of nicotine in humans is primarily diurnal, peaking at midday, with spikes of increased clearance after meals, which is concordant with increased human smoking rates early in the day, lowest smoking rates in the evening, and increased smoking after meals *(61)*.

P450 2A6 activity varies approximately 50-fold in humans as measured by analysis of protein levels and in kinetic experiments with liver samples *(58,62,63)*. The basis for constitutive differences in activity has been associated with variant CYP2A6 alleles encoding inactive enzyme *(62,64–67)*. A statistically significantly reduced frequency of two CYP2A6 null alleles in nicotine (and alcohol)-dependent smoking-clinic patients versus never nicotine-dependent individuals and a statistically significant negative association with the numbers of cigarettes smoked per week have been reported *(68)*. This study needs to be replicated in additional samples to confirm the possible role of inherited variation at the CYP2A6 locus in smoking behavior.

Misspecification of the CYP2A6 genotype because of incompletely specific CYP2A6 genotyping assays *(64,67)* may affect the statistical significance of findings relating CYP2A6 alleles to smoking behavior.

Plasma and urinary nicotine and cotinine concentrations have repeatedly been found to be associated with the number of cigarettes smoked per day *(69–71)*. Since cotinine has a half-life an order of magnitude greater than that of nicotine, it is useful as a biomarker in smoking surveys, smoking cessation trials, and the assessment of exposure to environmental cigarette smoke *(72,73)*. Interindividual variation in the conversion of nicotine to cotinine and in the clearance of cotinine may have effects on nicotine consumption and dependence *(53)*. For example, cotinine levels were found to be higher in African-Americans than in Caucasian-Americans or Mexican-Americans, after adjustment was made for reported cigarette smoking *(74)*. While nicotine metabolism was not found to be statistically significantly different in African-Americans and Caucasian-Americans, mean nonrenal and total metabolism (clearance) of cotinine was shown to be significantly lower in African-Americans than in Caucasian-Americans *(74,75)*. Calculation of nicotine intake per cigarette on the basis of the inpatient infusion studies also indicates that African-Americans absorb statistically significantly more nicotine per cigarette smoked than do Caucasian-Americans *(75)*. This suggests that differences in the numbers of cigarettes smoked among African-American and Caucasian-American smokers *(76,77)* may be influenced by metabolic differences between the groups.

Genetic Factors Associated With Cigarette Smoking

Evidence for genetic determinants affecting the smoking phenotype has steadily accumulated both from studies of substance abuse in animals and from analysis of the contributions of genetics and personality to substance abuse in humans *(78,79)*. Two recent linkage studies in humans *(80,81)* have indicated regions of the genome in which loci affecting nicotine dependence and ever smoking may be found with further work. However, an appreciation of the neurotransmitter-related mechanisms involved in reward circuits in the human brain has suggested many candidate loci potentially associated with nicotine dependence *(54)*. The first genetic association studies in humans at dopaminergic loci *(82–88)* have reported statistically significant differences in the allele frequencies between smokers and nonsmokers at markers linked to the genes coding for the D1, D2, and D4 dopamine receptors and at the dopamine transporter, consistent with the dopaminergic reward hypothesis of nicotine dependence *(89)*.

As in some previous studies of the D2 dopamine receptor in case–control studies of substance abuse *(90)*, the less frequent allele (A1) at a genetic marker flanking the dopamine receptor D2 coding sequence (DRD2) was found to be at a higher frequency in the collections of smokers versus nonsmokers *(82,83)*. In a sample of smokers undergoing a limited smoking cessation intervention, a protective association with a particular allele (allele 9) at the dopamine transporter (SLC6A3) was observed with smoking status, age at smoking initiation, and history of quitting, and the protective association with smoking status was stronger in those individuals with DRD2 A2 genotypes *(88)*. Since the DRD2 A1 allele has been found previously to be associated with lower D2 receptor densities *(91)* and the SLC6A3 allele 9 has been associated with excess dopamine after cocaine abuse *(92)*, this suggests that the protective association with smoking status observed may be due to normal densities of DRD2 receptors and increased synaptic dopamine that may provide some resistance to nicotine dependence *(88)*. At the D4 dopamine receptor locus, allele DRD4.7, found previously to be associated with novelty seeking and substance abuse in some case–control studies *(93)*, was found in African-Americans, but not in Caucasian-Americans, to be associated with smoking status, intensity, persistence, and initiation. In Caucasian-Americans, a statistically significant association of allele 4 of the DRD4 receptor (not associated with novelty seeking) with smoking for the regulation of mood in depressed smokers was observed *(87)*, suggesting that the DRD4 locus may affect smoking behavior in depressed individuals as well as increase vulnerability to nicotine dependence in some populations *(86)*. These preliminary candidate gene studies need to be repeated in larger samples, in samples with similar and different ethnic origins, and in family-based samples to confirm the effect of these alleles on vulnerability to nicotine dependence, to explore the effect in samples that differ in allele frequency and smoking prevalence, and to control for potential confounding in case–control samples. Future studies involving neurobiologic candidate loci that potentially affect smoking behavior should also emphasize the analysis of functional genetic polymorphisms or of linkage disequilibrium structure to identify haplotypes potentially carrying functional polymorphisms *(94)*.

Genetic epidemiologic studies using the twin-study design *(95)*, where multiple genetic and environmental risk factors and a threshold disease model are modeled by use of concordance data in monozygotic and dizygotic twins, have estimated the effects of genetic and environmental factors on current smoking, smoking initiation, and smoking persistence *(96)*. A reanalysis of seven twin studies from Scandinavia, the United States, and Australia estimated that a mean of 60% of the variance in risk of being a current smoker in men and women is accounted for by additive genetic effects, with most studies demonstrating statistically nonsignificant shared environment effects *(96)*. From the same studies, the mean additive genetic effect on the liability to smoking initiation (i.e., becoming a smoker) was estimated to be 57%, with an estimated mean shared environmental effect of 17%. From three of the studies where data were available to assess the relative contributions to smoking persistence, the mean additive genetic effect was estimated to be 69%, with statistically nonsignificant estimated shared environmental effects. A recent analysis of smoking initiation and persistence among twin pairs in the Vietnam Era Twin Registry found that the best-fitting model included statistically significant additive genetic factors (explaining 50% of variance in risk) and both shared (family, 30% of variance) and specific (to one twin) environmental factors (20% of variance) for smoking initiation. For smoking persistence, however, only genetic and specific environmental factors were found to be statistically significant, explaining approximately 70% and 30% of the variation, respectively *(97)*. Thus, twin studies estimate that the majority of the liability to become and to remain a smoker is explained by additive genetic factors. A variable remaining portion of the risk is estimated to be related to specific environmental effects, but there is no consistent, statistically significant evidence for a shared or common environment effect.

To assess whether the decline in smoking initiation in men

and the increase in smoking initiation in women have led to a change in the interaction of genetic and environmental effects with birth cohort, three large twin studies were reanalyzed that covered birth cohorts from the early 1900s to the mid-1960s *(98)*. Researchers tested heterogeneity of twin tetrachoric correlations across samples and across sex and found increased genetic effects in men in two of the samples compared with the third sample; however, there was no genetic heterogeneity by age cohort *(98)*. The modeling of age-related changes in the effects of genetic and environmental factors in smoking initiation in adolescent twin pairs showed that genetic effects increased with age; however, shared environmental effects, which explain the majority of variation in risk at early ages (12–16 years), were not statistically significant in early adulthood *(99)*. Family studies of the relatives of substance-dependent individuals ascertained in treatment settings, with control subjects located via a random-digit-dialing protocol, suggest that there are both general factors increasing vulnerability to substance abuse and specific factors increasing vulnerability to specific drugs, including habitual smoking *(100)*. Family studies of the siblings of alcoholic and nonalcoholic probands ascertained in treatment and nontreatment settings identified the sibling's own sex, birth cohort, and comorbid substance dependence as statistically significant predictors of habitual smoking (defined as a smoking history of $\geqslant$20 cigarettes per day for $\geqslant$6 months) *(101)*. Only habitual smoking in the proband, but not other substance abuse, was a statistically significant predictor of habitual smoking in siblings, suggesting a specific risk factor for nicotine dependence.

Smoking Motives, Personality Factors, and Nicotine Dependence

Personality and behavioral studies have suggested why some people are more likely to smoke and what smokers perceive that they derive from smoking tobacco. Research in motives for smoking posits a limited number of factors based on responses to questions concerning hypothesized reasons for smoking *(102–104)*. These factors have been constructed from psychosocial models of various motives for smoking, such as smoking to modify affect, smoking to relax, food substitution smoking, etc. *(105)*. Investigation of the correlation structure among these hypothesized motives for smoking provided consistent and statistically significant support for six of these factors: addiction, automatic, stimulation, psychosocial, indulgent, and sensorimotor manipulation *(105,106)*. Interfactor correlation analysis suggested that the first three factors loaded onto a second-order pharmacologic factor and the last three loaded onto a nonpharmacologic factor *(106)*.

Smokers experience self-reported increases in arousal and decreases in stress after smoking cigarettes, with absolute levels of arousal and stress peaking in midday and in the morning, respectively *(107)*. Smokers experience stimulation and sedation simultaneously from each cigarette; however, they also experience lower equilibrium levels of arousal and higher equilibrium levels of stress than nonsmokers. After smoking cessation, mean arousal and stress levels are increased and reduced, respectively, suggesting that smoking cigarettes may contribute to the increased stress observed in smokers *(108)*.

Personality and temperament constructs that use questionnaires to measure heritable personality dimensions quantitatively, e.g., Cloninger's Tridimensional Personality Questionnaire *(79,109)*, have been used to investigate personality traits. Novelty seeking, extraversion, impulsivity, and neuroticism have been identified as the personality factors found at higher levels among smokers than among nonsmokers *(110–113)*. That both dependent and nondependent smokers exhibit similarly increased sensation-seeking scores relative to nonsmokers suggests that, while increased sensation-seeking may increase liability to smoking initiation, it may not be related to differences in nicotine dependence among smokers.

Fagerstrom and colleagues proposed an eight-question "Tolerance Questionnaire" (FTQ) in 1978 *(114)* and a revised questionnaire *(115)*, the Fagerstrom Test for Nicotine Dependence (FTND), in an attempt to provide quantitative information on nicotine dependence to assist in cessation therapy. FTQ and FTND scores have been found to show statistically significant associations with biochemical measures related to the quantity of cigarettes smoked (plasma nicotine, plasma or urinary cotinine, and expired CO) and are also associated with cessation outcome in trials without nicotine replacement therapy *(115,116)*. FTQ and FTND scores have not been consistently correlated with percent abstinent at the end of the placebo-controlled trials with nicotine-replacement therapy; when they are predictive, they explain only 1% of the variation *(116,117)*. FTND scores from population-based samples of smokers are statistically significantly lower than scores from smokers seeking cessation help *(118)*.

A small fraction of active cigarette smokers are known as chippers or nondependent smokers, defined as smoking five or fewer cigarettes per day *(119)*. Compared with regular smokers, chippers were found to extract similar amounts of nicotine per cigarette and to exhibit similar elimination half-lives of nicotine but to be statistically significantly less nicotine dependent and to have begun their smoking careers significantly more slowly *(119–121)*. Regular smokers scored higher on pharmacologic smoking motive factors, and chippers scored higher on nonpharmacologic smoking motive factors *(122)*. Chippers and regular smokers both appear to smoke for affect management; however, unlike regular smokers, chippers do not crave cigarettes and exhibit lower levels of smoking for stimulation and smoking to relieve negative affect.

The establishment of nicotine dependence in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders (DSM)*, third edition, represented the nosologic and diagnostic recognition of this drug dependency *(123)*. The DSM-III/DSM-IV diagnosis of nicotine dependence (305.10) requires a minimum of three of seven diagnostic symptoms: tolerance, withdrawal, greater use than intended, persistent desire to quit, great amounts of time spent smoking, activities given up or reduced due to smoking, and continued smoking despite knowledge of having a persistent physical or psychologic problem with the substance *(123,124)*. The DSM-IV diagnosis of nicotine withdrawal (292.0) requires four or more symptoms of eight to appear after abrupt cessation of tobacco use *(124)*. A diagnosis of nicotine abuse is not recognized in either the DSM-III-R or the DSM-IV, primarily because nicotine does

not meet two of the major criteria for a diagnosis of substance abuse. Specifically, nicotine is not considered to produce intoxication, and a diagnosis other than nicotine dependence would not be appropriate for maladaptive use of the substance *(125)*. Nicotine dependence is a model for drug dependence, where tobacco smoking fulfills the physiologic, behavioral, and social characteristics of a dependence syndrome, but it also acts as a gateway drug for other drugs of abuse *(126)*. However, the morbidity and mortality due to the direct effects of tobacco smoking exceed the direct or indirect effects of other drugs of abuse or, indeed, of any other single behavior on a population level *(2,127)*. In contrast to the FTQ/FTND, there are no explicit quantitative measures assessed in the DSM substance dependence criteria, which are derived from the alcohol-dependence syndrome, a gradient of the severity of dependence comprising additional behavioral elements rather than increased consumption per se *(128–130)*. Analysis of the factor structure of DSM-III-R nicotine dependence identified two factors named "general dependence" and "failed cessation," suggesting that DSM-III-R nicotine dependence is composed of multiple psychopharmacologic mechanisms that may differ in strength among smokers *(131)*.

Among 15- to 54-year-old civilian, noninstitutionalized Americans (n = 4414) surveyed for tobacco use in the National Comorbidity Survey in 1991, lifetime DSM-III-R nicotine dependence was found at a population prevalence of 26% in men and 23% in women and at a higher prevalence among at least one-time tobacco users, i.e., 33% among males and 31% among females *(132)*. With the use of data from the 1991–1992 National Household Survey on Drug Abuse (NHSDA) data (n = 61 426), of those who used cigarettes on a daily basis (n = 10 383), 91% experienced one or more symptoms of nicotine dependence; when grouped by cigarettes smoked per day, the frequency of those reporting symptoms of dependence was dose related *(133,134)*. Among middle-aged, male daily smokers (n = 1006) from the Minneapolis–St. Paul area surveyed in 1982, 90% were found to qualify for DSM-III nicotine dependence *(135)*. Among ever users of tobacco, defined as those who had used tobacco at least six times (n = 645), in a survey from the DSM-IV field trials using clinical populations in 1992 *(136)*, 87% qualified for provisional DSM-IV nicotine dependence. DSM-III-R nicotine dependence occurs in 56% of daily smokers in an 18-year-old New Zealand sample (n = 321) and in 51% of daily smokers in a young-adult Michigan sample (n = 381) *(137,138);* however, very large samples of adolescent smokers have not been studied. While consumption and dependence are statistically significantly associated for all drugs of abuse, tobacco is similar to cocaine and the opiates in terms of its addiction liability; i.e., most users are dependent, in contrast to users of alcohol, amphetamines, and cannabis *(136,184)*. For example, among last year users of alcohol (n = 54 998), nicotine (n = 28 392), cannabis (n = 11 237), and cocaine (n = 3410) in a nationally representative U.S. population sample (1991–1993 NHSDA), nicotine users were statistically significantly more likely to be nicotine dependent (28%) than alcohol (5.2%), cannabis (8.2%), or cocaine (11.6%) users *(184)*. Also, only about 6%–12% of current smokers are intermittent (never daily) smokers *(139);* thus, the vast majority of cigarette smokers are daily smokers and, of these, the majority are nicotine-dependent smokers by DSM-III-R or DSM-IV criteria.

Smoking, Psychiatric Comorbidity, and Substance Use

Statistically significant associations have been found in different young adult and adult samples between smoking and depression, anxiety, and alcohol dependence. A randomized trial of clonidine in heavy smokers provided a provocative etiologic link between depression and smoking that led to a number of cross-sectional and prospective studies *(140)*. With the use of data from the 1980–1983 St. Louis (MO) NIMH-Epidemiologic Catchment Area (NIMH-ECA) Survey, ever smoking was found to be statistically significantly more prevalent in those with major depression and with DSM-III alcohol dependence (adjusted for major depression) than in those with no DSM-III diagnoses *(141)*. With the use of data from the 1975 National Health and Nutrition Examination Survey and the Center for Epidemiologic Studies Depression (CES-D) scores, current smoking was found to be significantly related to CES-D score *(142)*. In a random-digit-dialing telephone study of Latinos, current smokers were found to have higher mean CES-D scores and were statistically significantly more likely to have experienced depressive symptoms than never smokers *(143)*. In a smoking-cessation study sample, statistically significantly more smokers scored over the CES-D cutoff for depression than in a general population sample; depressed smokers scored statistically significantly higher on the FTND than those below the CES-D cutoff *(144)*. With the use of data from the 1981–1983 Durham (NC), NIMH-ECA Survey, current smoking was found to be statistically significantly more prevalent in those with DSM-III generalizable anxiety disorder and DSM-III alcohol dependence but not in those with DSM-III depression. These findings could result from a lack of power, since the prevalence of depression observed in the Durham survey was half that seen in the St. Louis survey *(145)*. In a sample of 21- to 30-year-old members of a health maintenance organization (n = 1007), smoking was found to be statistically significantly associated with other drug dependencies, major depression, and anxiety disorders *(146)*. Furthermore, when adjusted for the presence of depression and anxiety disorders, moderate (five to six of the criteria met) but not mild (three to four of the criteria met) nicotine dependence was associated with a statistically significant increase in risk for all other drug dependencies compared with nondependent smoking *(138)*. Similarly, when adjusted for other drug dependencies, both mild nicotine dependence and moderate nicotine dependence significantly elevate risk for major depression, although not for any anxiety disorder *(138)*. In a 14-month follow-up period in this young adult sample, the presence of major depression in current smokers resulted in an increased risk of becoming nicotine dependent or to progress from mild to moderate nicotine dependency *(147)*.

An unresolved problem in the established association between depression and smoking is the issue of causality, since the potential for self-medication or precipitation of depression on cessation is inherent in the modulating effects of nicotine on neurotransmitter systems *(24)*. For example, tobacco smoke, but not nicotine administration, statistically significantly reduces levels of monoamine oxidases A and B, which are essential metabolic enzymes for many neurotransmitters *(148,149)*, suggesting that other components of tobacco smoke may have a substantial effect on synaptic dopamine concentrations *(150)*. Multiple methods were used in a sample of female twins to

assess possible causal relationships between the statistically significant and reciprocally associated diagnoses of nicotine dependence and major depression in co-twins and in their families *(151)*. With the use of the co-twin control method that compares observed and expected rate differences between monozygotic and dizygotic twins, observed concordances rejected a causal model for one DSM-III-R diagnosis causing the other; in contrast, either a noncausal family environment or a noncausal genetic model fits the observed data. Modeling of genetic and environmental factors indicated a statistically significant genetic correlation between the liabilities to smoking and major depression, with specific environmental factors affecting the liabilities independently and a common environmental factor influencing the liability to smoking only *(151)*. These data suggest that common genetic factors may contribute to both daily smoking and major depression.

The relationship between tobacco and alcohol use and abuse has been the subject of comprehensive reviews *(126,152,153)*. Smoking and alcoholism are statistically significantly associated in population samples; e.g., 38% of ever smokers met the definition of DSM-III-R alcohol abuse and/or dependence versus only 16% of never smokers in a young Michigan sample *(154)*, while 20% of ever smokers met the definition of DSM-III-R alcohol abuse and/or dependence versus only 8% of never smokers in a North Carolina NIMH-ECA sample *(145)*. DSM-III-R-defined nicotine dependence and alcohol dependence were statistically significantly associated with each other, with the association at the same level as that with major depression and anxiety, i.e., odds ratios of 2–4 *(146,154–156)*. A statistically significant association between the severity of DSM-III-R alcohol dependence (as defined by numbers of positive criteria) and nicotine dependence (as defined by FTQ score) was observed in a clinical (alcohol treatment) population where 88% of the alcohol-dependent individuals are current smokers and 92% of these smokers are defined as nicotine dependent by FTQ score *(157)*.

Modeling of the statistically significant associations between alcohol use disorders and nicotine dependence in a university-based sample followed prospectively for 7 years, with individual diagnostic data and family history interview data, supports both reciprocal influence and common vulnerability models *(158)*. Modeling of joint alcohol and tobacco use in a twin sample consisting of two age groups found that shared environmental factors are most important in early use (ages 12–16 years) and that genetic factors are more important in later use (ages 17–25 years) *(99)*. More important, the shared correlation for the effect of genetic factors, which explain approximately 50% of the alcohol use and 50% of the tobacco use in older adolescents and young adults, is nearly unity, suggesting that substantially the same genetic factors are operating in this sample to influence both alcohol and tobacco use *(99)*. With the use of the NAS-NRC World War II Twin Registry to investigate the genetic effects on multiple substance use, a twin model with a common genetic pathway to tobacco, alcohol, and coffee use, with no environmental effects and separate pathways with both genetic and shared environmental effects for each substance, provided the best fit to the data *(159)*. Most of the genetic effect on tobacco consumption was found in the common genetic pathway, and most of the genetic effects on alcohol and coffee consumption were found in substance-specific pathways. Regression analysis of heavy consumers of the three substances in the NAS-NRC Twin Registry found two independent latent factors, one underlying heavy smoking and heavy alcohol use and one underlying heavy smoking and heavy coffee drinking *(160)*. Separate factors contributing to the comorbidity of alcohol and nicotine dependence and to the comorbidity of nicotine dependence and coffee drinking may reflect independent regulation of the multiple pharmacologic effects of nicotine and the paired substance *(161)*.

Demographic and Social Environment Factors and Cigarette Smoking

Prevalence surveys indicate that some demographic variables—sex, age, ethnicity, and socioeconomic status (SES)—are consistently associated with cigarette smoking. Specifically, male sex, younger age, lower SES, and lower educational attainment are positively associated with current smoking prevalence, while Hispanic and Asian/Pacific Islander ethnicity is negatively associated with current smoking prevalence *(11,13,15,77,162)* . However, while the negative association between educational attainment and smoking prevalence is consistently observed in diverse population samples in the United States *(163)*, some non-U.S. populations show a reverse association, e.g., among females in Italy *(164)*.

In the United States, over the period from 1965 through 1994, current smoking prevalence among adults less than 65 years of age has decreased in every demographic category except those with less than 12 years of education *(9)*. In those adults greater than or equal to 65 years of age, stable to increased rates of current smoking are observed in those with less than 12 years of education, in women, and in African-Americans *(9)*. The quit ratio, defined as (former smokers)/(ever smokers), has increased in all groups; however, the rate of increase of the quit ratio has been slower in adults 65 years old or older. Combined with the postwar demographic bulge, the absolute number of older current smokers continues to increase despite a long-term decrease in smoking prevalence over the 30 years from 1965 through 1994.

The relationship between SES and smoking is complex, involving a number of related factors. The statistically significantly increased risk of smoking prevalence in those below the poverty threshold *(14)* is concordant with a statistically significantly increased risk for the opportunity of exposure to tobacco products over the age period 6–13 years because of neighborhood disadvantage, at least in Baltimore (MD) *(165)*. In this same city, reduced levels of parental monitoring [statistically significantly associated with male sex of the child, reduced educational achievement, and a history of psychiatric disorder in mothers *(166)*] are statistically significantly associated with increased risk of smoking initiation *(167)*. Cigarette acceptability and accessibility were the only school and neighborhood measures statistically significantly associated with cigarette smoking rates in a study of Midwestern elementary schools *(168)*. However, neighborhood disadvantage is not always associated with increased rates of cigarette smoking; adjusted for attitude toward substance use and availability (including cigarettes), neighborhoods with lower population density, suggesting economic advantage, had higher rates of lifetime cigarette use in this Midwestern sample *(168)*.

Intensive marketing of tobacco products has likely played an important role in establishing the prevalence of smoking observed today. Targeted promotion may be responsible for a men-

thol cigarette brand being the most prevalent brand among African-American smokers and for brand recognition among adolescents *(2,169–171).* Publication of a cigar-oriented magazine, endorsement of cigar use by celebrities, and marketing to high SES consumers may have reversed a 20-year decline in cigar consumption, the beginning of which coincided with advertising bans enacted in 1969 and 1973 *(172).*

There is evidence, however, that a number of social environmental factors, especially at the regulatory level, have been working to decrease the prevalence of smoking. Increasing societal disapproval of smoking since the 1964 Surgeon General's Report *(173)* has resulted in workplace regulation of smoking, among other antismoking sanctions *(174).* However, a national survey of 1992–1993 indoor workplace smoking policies reported by workers themselves observed statistically significantly different levels of workplace smoking restrictions by sex, age, smoking status, and occupation of the worker *(175).* These differences found between these sociodemographic factors and workplace smoking restrictions parallel differences in smoking prevalence by sex, age, and educational attainment. Recent U.S. Food and Drug Administration regulations and measures included in the first states' attorneys' general tobacco settlement were designed to modify the marketing behavior of the tobacco companies to susceptible youth populations and to contribute to smoking cessation programs *(176,177).* Analysis of media campaigns designed to reduce smoking initiation and to increase smoking cessation has demonstrated statistically significant associations between targeted media and reduced rates of smoking in adolescent females *(178).* A combination of a large state tax increase and tobacco control measures that included prevention, cessation, and environmental tobacco smoke programs was associated with an increased average quarterly decline in cigarette sales, during a period in which average levels of educational attainment and income were decreasing *(179).*

Summary

The estimated number of worldwide current smokers of both sexes in 1996 exceeded one billion individuals *(20).* Research into smoking behavior and pharmacology has established that most smokers are smoking to maintain nicotine levels *(30,45).* Recent neurobiologic research *(24)* has established the proximate molecular neurobiologic substrate of the mechanism that maintains nicotine addiction. Nicotine dependence is significantly associated with substance abuse, anxiety disorders, and affective disorders *(141,155,180).* Twin-model analysis of the genetic and environmental factors affecting smoking initiation, current smoking, and persistence reveals that heritability is stable and more important than environmental factors *(96).* However, major secular changes in smoking prevalence support strong effects of environmental determinants on smoking behavior *(175),* as do consistent demographic predictors such as educational attainment in the United States *(13).*

Nicotine dependence, major depression, and alcohol dependence are the three most prevalent specific psychiatric diagnoses in population samples in the United States, while substance abuse, anxiety disorders, and affective disorders are the three most prevalent diagnostic categories *(132,180).* Nicotine dependence is significantly associated with each of these three categories, an example of the striking concentration of psychiatric comorbidity in approximately one sixth of the U.S. population *(180).* The increased severity of nicotine dependence within the U.S. smoking population *(118)* and among those with psychiatric comorbidity *(181)* suggests that smoking cessation programs may be negatively affected *(182),* as has been observed *(141,144).* While it is the contamination of the nicotine delivery device with carcinogens, carbon monoxide, and cytotoxic compounds that is the probable source of the attributable risk from smoking in cancer and cardiovascular and respiratory diseases, an improved understanding of the neurobiologic mechanisms that maintain nicotine dependence may provide the basis for reducing morbidity and mortality, through improved smoking cessation therapies. Methods to incorporate covariates known to be significantly associated with smoking prevalence and behavior, including age, sex, SES, psychiatric history, and previously identified genetic loci, should be used in future candidate gene studies. Research sample design and future analyses of the smoking phenotype must address the consistent, statistically significant risks due to demographic, psychiatric, and genetic factors to improve our understanding of the socioeconomic, psychosocial, and neurobiologic bases of this behavior.

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NOTES

[1]The *O*-glucuronide metabolite of NNAL (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol), a metabolite of one of the principal pulmonary carcinogens in tobacco smoke, NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butone.

[2]The contemporary Centers for Disease Control and Prevention categories of cigarette smokers are current smokers (defined as those who currently smoke every day or on some days), former smokers (ever smokers who do not currently smoke every day or on some days), and never smokers (who have smoked fewer than 100 cigarettes in their lifetime) *(11)*.

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